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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/196,154	11/16/95	LIVINGSTON	P 43016-A-PCT-

EXAMINER
CAPUTA, A

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/196,154	Applicant(s) Livingston et al.
	Examiner Anthony C. Caputa	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Jul 21, 1995*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *21-43*

Of the above, claim(s) _____ is/are pending in the application.

☐ Claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *21-43* is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claims _____ is/are objected to.

_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 8

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

Part III DETAILED ACTION

1. The disclosure is objected to because of the following informalities:

On page 5, line 30, in Brief Description of the Figures, Figure 6b is listed as IgG antibodies but Figure 6b has the y-axis labeled as IgM titer.

Appropriate correction is required.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3. Claims 21-29 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 44-52 of copending application Serial No. 08/477,097 or 08/475,784. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

4. Claims 30-42 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 44-56 of

copending application Serial No.08/477,147 and 08/481,809. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

5. Claims 21-29 of this application conflict with claims 44-52 of application serial numbers 08/477,097 and 08/475,784.

Claims 30-42 of this application conflict with claims 44-56 of copending applications serial numbers 08/477,147 and 08/481,809.

37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See M.P.E.P. § 822.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 21-29, and 43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting

as being unpatentable over claims 44-56 of copending application Serial Nos. 08/477,147 and 08/481,809. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims as recited in the copending applications encompass the composition as instantly claimed.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 30-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44-52 of copending application Serial Nos. 08/475,784 and 08/477,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims as recited in the copending application encompass the composition as instantly claimed.

Claim Rejections - 35 USC § 112

8. Claims 21-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is rejected for being vague and indefinite for using the trademark "QS-21" since it is unclear what the metes and bounds of said trademark. Since a product denoted by a trademark may at some time change it is suggested the trademark be accompanied with the generic terminology. See MPEP 608.01(v).

Claim 35 is indefinite because they contain the abbreviation "QS-21". Full terminology should be in each instance in the claims without the additional use of redundant abbreviations in parentheses or otherwise. Correction is required.

Claims 21-43 are rejected since they refere to claims which have been cancelled.

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph as failing to adequately teach how to make and/or use the invention, i.e failing to provide an enabling disclosure.

The specification teaches a method for preparing GD3 and GM2 ganglioside conjugate vaccines. The specification also teaches that immunization of mice with the GD3-Keyhole Limpet Hemocyanin (GD3-KLH) conjugate generated the highest titer of IgM and IgG responses compared to the other conjugates tested and that the sera was highly specific for GD3 in human tissue extracts. The specification teaches that melanoma patients immunized with the GM2-KLH generated high titers of IgM and IgG antibodies. The specification does not teach that the production of antibodies to GD3-KLH or GM2-KLH results in the treatment of the cancer. The production of antibodies upon administration of a ganglioside conjugate vaccine cannot be extrapolated to the ability of the antibodies to prevent or treat cancer since in a previous study, no significant prolongation of survival was observed in mice that were administered a GM2-KLH conjugate vaccine, despite the ability of GM2-KLH to produce of high titers of anti-GM2 IgG antibodies (see Fung et al, Cancer Research 50:4308-4314, 1990 on p 4312, column 2, paragraph 2). Therefore, the production of antibodies upon administration of a ganglioside conjugate vaccine is not sufficient to insure that these antibodies will prevent cancer.

The specification also does not provide guidance on the synthesis of conjugates with other gangliosides or chemically

modified gangliosides. As described in the specification the ganglioside region of attachment to the carrier protein is important in maintaining the antigenicity of the ganglioside. Due to the variations in both the carbohydrate and ceramide portions of various gangliosides, it is not clear if the method used to conjugate GD3 and GM2 to KLH could be applied to other gangliosides and still maintain the antigenicity of other gangliosides. The specification also does not provide guidance on the synthesis of derivatives of KLH not does the specification teach which derivatives would result in an enhanced antibody response.

10. Claims 21-43 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12.

Claims 21, 26-34, 36, and 39-43 are rejected under 35 U.S.C. § 103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. Pat. No. 5,102,663) and Ritter et al (1990).

Livingston et al. teach a vaccine administered to melanoma patients for stimulating the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (p 7046-7048). Livingston et al teach that the vaccine is administered at a concentrations of 100, 200, or 300 µg with an adjuvant, *Bacillus* Calmette-Guerin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046 column 1 paragraph 3 and paragraph bridging p 7046 and 7047). Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination (p 7048 paragraph 1 and column 2, paragraph 2). Livingston et al. teach that more patients produced IgM antibodies that IgG antibodies to the GM2 (p 7047 paragraph bridging columns 1 and 2). Livingston et al. also teach the gangliosides GM2, GD2, and GD3 are expressed on the cell surface of human malignant melanomas (p 7045, column 1 paragraph 2).

Livingston et al do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH). Livingston et al also do not teach the use of any other gangliosides in a vaccine preparation.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p 406, paragraph 1). Ritter et al discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediate antibody-dependent cell-mediated cytotoxicity; d) and is generally detectable in the serum for longer periods after immunization. Livingston et al (U.S. Pat. No. 5,102,663) teach that the gangliosides GM3, GM2, GD3, GD2, GT3, and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1 lines 22-28). Ritter et al (1990) teach that GD3 derivatives such as GD3 lactone are more immunogenic that GD3 (abstract).

It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al. by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages taught above by Ritter et al (1991). It would have also have been obvious to substitute any of the gangliosides GM3, GD2, GD3, GT3 or O-acetyl GD3 for the GM2 ganglioside in the vaccine because they are all prominent cell-membrane components of melanoma as taught by Livingston et al (U.S. Pat 5,102,663) and one of ordinary skill in the art would expect that IgG antibodies against these gangliosides would react with the melanoma cells. It would also have been obvious to substitute GD3 lactone for the GM2 ganglioside in the vaccine because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990), and would be expected to produce and enhanced antibody response compared to GD3.

Optimization of the dosage, route of adminstration, and number of sites to administer the composition is within the skill of the ordinary artisan.

13. Claims 35 is rejected under 35 U.S.C. § 103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) as applied to claims 21, 26-34, 36, and 39-43 above, and further in view of Kensil et al and Marciani et al.

The teachings of Livingston et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) are set forth above. The above cited art does not teach the use of QS21 as an adjuvant.

Kensil et al teach that QS21 produced a higher antibody response that aluminum hydroxide (p 433, column 2, paragraph 4 and Fig. 3). Kensil et al also teach that the immune responses obtained with QS21 reached a plateau at doses between 10 and 80 µg in mice (p 433, column 1, paragraph 3). Marciani et al teach the use of QS21 as an adjuvant in a vaccine at concentrations of 10 and 20 µg (p 91, column 2, paragraph 4 and p 93, paragraph 1). Marciani et al also teach that the QS21 adjuvant did not cause a toxic reaction in cats (p 93, paragraph 1).

It would have been obvious to one of ordinary skill in the art to add QS21 as an adjuvant to the vaccine taught by the above cited art because QS21 produces a higher antibody response than the commonly used adjuvant, aluminum hydroxide, as taught by Kensil et al, and QS21 is not toxic to animals as taught by Marciani et al. It would also have been obvious to use doses of between 10 and 200 µg because the immune response obtained with QS21 plateaus at doses between 10 and 80 µg and optimization of the dose according to the subject receiving the vaccine is within the skill of the ordinary artisan.

14. Claims 22-25, 37 and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) as applied to claims 21, 26-34, 36, and 39-43 above, and further in view of Irie et al.

The teachings of Livingston et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) are set forth above. It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach administration of the vaccine for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

Irie et al teach that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31). It would have been obvious to one of ordinary skill in the art to administer the vaccine taught by the above cited art to patients afflicted with or susceptible to cancer of an epithelial origin (e.g. breast carcinomas) because the ganglioside GM2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the vaccine react with the tumor and either treat or prevent the cancer.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony Caputa whose telephone number is (703) 308-3995. The Examiner can be reached Monday through Thursday 8:30am to 6:00pm, E.S.T.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ANTHONY C. CAPUTA
PATENT EXAMINER
GROUP 1800

Anthony C. Caputa, Ph.D.
June 12, 1996

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